Utilisation and outcomes of treatment in Autism Spectrum Disorder

Valorisation addendum

Valorisation refers to the process of transferring purely scientific knowledge gained in academic studies into value for broader societal purposes. Results of this thesis are discussed in this context in this appendix.

Healthcare problem

Autism is a neurodevelopmental condition which can have a tremendous impact on the affected person as well as other members of the family. Around 2% of people in the USA are diagnosed with autism today and it is known to affect people of all geographies and ethnic, cultural and racial backgrounds. The main symptoms are difficulties with verbal and non-verbal communication, difficulties understanding social or emotional cues, and the desire to carry out simple and repetitive tasks. Other common difficulties — faced by some, but not all people with autism — include attention deficits, depressive thoughts, anxiety, sleep problems, irritable and aggressive behaviours, and obsessions, among others. The wide variety of symptoms in autism is what prompted Dr Stephen Shore – a special education professor with autism - to say, "If you've met one person with autism, you've [only] met one person with autism." In other words, autism effects different people in different ways. This also the reason for the coining of the term autism "spectrum" disorder, or ASD for short.

Today, there are no drugs to treat autism's core symptoms. Instead, the majority of recommended treatments are based on individualised behavioral or social-developmental therapies. There are however concerns that not all children with autism have the same access to such therapies. For example, in the USA, there have been historical concerns that children in rural areas, or on private healthcare plans, find it harder to access these treatments.

The fact that most recommended treatments are non-drug based, does not mean that people with autism do not take drugs as well. In fact, prior to the start of this thesis, estimates were that around 42% of autistic children and 62% of autistic adults use psychotropic drugs (drugs that effect the brain). These numbers are mainly based on data from North America however, and the studies on adults did not include many people.

With the widespread use of psychotropic medications in ASD comes concerns about potential safety effects, especially in children. For example, stimulants and atomoxetine (used to manage attention deficits), are known to increase blood pressure and heart rate, which in turn has raised concerns about the possible increased risk of more serious cardiovascular events such as stroke, heart attacks, or severe irregular heartbeats. Antipsychotics (used to manage behavioral difficulties in ASD) have previously been associated with increased bone fracture risk in elderly dementia patients, but it is unclear if this is also the case in children with autism.

In terms of testing new treatments for autism, there is little agreement on how to measure which treatments are most effective. Measures used in clinical trials are often time-consuming and expensive. It is often meaningful to understand how effective treatments are in "real-life" settings too, so cheaper and more sustainable ways to measure autism severity are needed. Given that parents of children with autism are often the main organisers and advocates for their child's treatment plan, a questionnaire of autism severity that can be completed by caregivers would be especially meaningful.

Main findings and implications of this thesis

This thesis comprised a collection of studies to address various problems and unanswered questions related to the use and outcomes of treatments in ASD, as mentioned above. All studies were based on either data from "real-life" settings using data that already existed in electronic medical records or insurance claims data, or by surveying caregivers of children with ASD.

The first set of results in this thesis examined levels of drug and non-drug treatment use in people with ASD. Having reliable treatment utilisation estimates is important for a variety of reasons. They can be used to quantify disease burden, inform health-economic and cost-benefit assessments of treatments, inform healthcare resource and training plans, measure the scale of certain risks (e.g. adverse events) and to aid planning for further research (such as defining eligibility criteria and interpreting results of new clinical trials). Other uses include identifying deviations from treatment guidelines or spotting differences in treatment approaches between countries, regions or healthcare plans, which can lead to additional understanding of underlying causes of deviations from guidelines, or if one healthcare system can learn from the other.

In this thesis, we found that drug treatment use is more prevalent in the USA (around 60% for children and 80% for adults) than in the UK (24% for children and 44% for adults). Differences in regulatory drug approvals likely explain some of the variation, but other factors such as differences in clinical guidelines, attitudes towards receiving drug treatment and differences in healthcare systems all deserve further exploration (which we began to do in Chapter 5). In time, results of our drug utilisation studies may provide important "baseline" data by which to assess the effectiveness of new policies aimed at either increasing or decreasing use of these drugs in the future. For example, since 2016 in the UK, a national program to stop "over medication" of all psychotropic drugs to people with ASD or intellectual disabilities, has been supported by NHS England. Additionally, our findings about other factors associated with increased treatment use, such as foster care and White race in the USA, and female gender in the UK should become the target of other future policy changes, to ensure equitable access to appropriate treatments for all.

For non-drug treatments, caregivers in the USA reported that almost all children (96%) received a non-drug treatment during a one-year period. We found no significant

differences in levels of treatment use between private and Medicaid (public) insurances, which is contrary to historical evidence of higher healthcare use in Medicaid, and supports the notion that recently introduced private insurance mandates have been effective at correcting historical advantages for accessing treatments via public plans. This evidence could be used to advocate for the introduction of similar mandates in other disease areas. Regarding geography, a significantly higher proportion of children in metropolitan areas versus non-metropolitan areas received SLT (72% vs 65%) and behavioural therapy (57% vs 46%). The most widely reported barrier to care in rural areas was a lack of available local services. Services like telehealth should be considered to address this gap in the future.

The second set of results in this thesis regarded safety concerns, as outlined above. Firstly, in two large case-control studies of children with ASD and attention deficit/hyperactivity disorder, we found no association between serious cardiovascular events and the current use of stimulants or atomoxetine. This finding should reassure the vast majority of physicians and parents, as well as a large number of patients who take these medications (around 14-19% children use one of these drugs annually). Further observational studies should focus on the subgroup of children with serious underlying cardiac abnormalities who were at increased risk however, and evaluate if their risk is independent of, or compounded by these medications. Until the evidence is clear, physicians should continue to note class-wide warnings and make careful cardiac evaluations in this vulnerable subset of patients prior to prescribing these medications.

Secondly, for fractures, we found a 40% lower risk of fracture for risperidone-exposed children compared to aripiprazole-exposed children. Risks were comparable between groups for the first 180 days on treatment, but significantly higher in the aripiprazole group thereafter, and even more pronounced for children less than 10 years old. If further studies corroborate our findings then this could deliver unique insights into the mechanisms by which antipsychotics have an impact on bone health, and eventually have impact in prescribing patterns in other disease beyond ASD too (for example, in schizophrenia and dementia). Nonetheless, until more is understood about these mechanisms and patients most at risk, patients and physicians should continue to use aripiprazole as usual but be aware of this signal. The information is certainly important and very clinically relevant, given that around 17% of autistic children use of these antipsychotics per year in the USA.

A final major contribution of this thesis was the validation of the Autism Impact Measure (AIM) as a reliable tool for measuring the severity of core autism symptoms. Given the variety of available interventions already being used by people with autism, plus new treatments in development, having reliable and accurate ways to compare treatment benefits is of critical importance for future decision making. This includes weighing up the benefits and risks of new treatments, by regulatory authorities, payers and providers of healthcare, and patients themselves.

As the AIM has distinctive benefits of being caregiver-relevant, quick and inexpensive to administer remotely, then it should be considered as tool for the real world monitoring of ASD symptoms, as well as in clinical trials. Through such a mechanism, the evaluation of different therapeutic approaches can inform treatment guidelines at a group level. It could potentially also allow rapid and direct feedback for effectively finding optimal treatment strategies on the individual level.

For the studies of non-drug treatment utilisation and validation of the AIM, we surveyed parents of children with ASD in the USA, via the Simons Foundation Powering Autism Research for Knowledge (SPARK) platform. SPARK is an online, USA-based research initiative for individuals with ASD and their family members. An intended and valuable benefit of conducting research via the SPARK online platform is that this offers a unique opportunity to engage the autism community directly in research, and to receive feedback on its relevance to them. Of the more than 5,000 caregivers surveyed, our research topic received an average rating of 4.8 out of 5 stars for its importance to them and their family. Once SPARK participant said, "I wanted to thank you for doing this study. We moved to a different state and we found vastly different therapies and available providers. This is a real problem for families."

The fact the SPARK platform as a whole has recruited 60,000 individuals with ASD and their families since forming in 2016 is testament to the incredible engagement and willingness of the ASD community to contribute to further research. All data from our studies in the SPARK cohort will be made available for linkage via the SPARK platform. The opportunity for future studies in the platform, either prospective or retrospective in nature, should not be missed.